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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/831,335	09/28/2001	Jacques Mallet	ST 98036-US-PCT	3243

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EXAMINER	
AKHAVAN, RAMIN	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 12/23/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Applicant's 12/27/04 RA

Office Action Summary	Application No.	Applicant(s)	
	09/831,335	MALLET ET AL.	
	Examiner	Art Unit	
	Ramin (Ray) Akhavan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 September 2004*.

2a)☒ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *20-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20-34,36 and 37* is/are rejected.

7)☒ Claim(s) *35* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *05/08/01*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Receipt of amendments/response, filed 09/30/2004, is acknowledged. Claims 1-19 are canceled and new claims 20-37 are added. Claims 20-37 are pending and under consideration in this action. Where applicable, a response to applicant's arguments with respect to any objection/rejections maintained, will be included in the body of the objection/rejection repeated herein. As new grounds of rejection are set forth herein that were not necessitated by amendments (Infra, §103 Rejection), this action is nonfinal.

Claim Objections

The following objections are necessitated by amendments to the claims. Claim 22 is objected to because of the following informalities: The claim is written without an article in front of the term "nucleic acid", thus is not a complete sentence. It would be remedial to include the article, "The". Appropriate correction is required.

Claim 35 is objected to under 37 CFR 1.75(c) as being in improper form because each claim is dependent from a multiple dependent claim (e.g. claim 29). See MPEP § 608.01(n). Accordingly, the claim 35 has not been further treated on the merits.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

1. **Claims 23-24, 26, 28-29 and 34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.**

The following rejections are necessitated by amendments to the claims or are the same grounds of rejection of record that are applied to the new claims:

Claims 23 and 24 recite the term, "moderate promoter". There is insufficient antecedent basis for this limitation in the claim. In addition, the term "moderate" is a relative term that is open to interpretation, thus making the claim vague and indefinite. As such the claims' metes and bounds are indeterminable.

Claim 26 is directed to several candidate proteins that can be expressed using the nucleic acid of claim 20, each of distinct structure or functionality. The claim recites that the protein is selected from group consisting of, "neurotransmitters or their precursors or enzymes for synthesizing them, and trophic factors". As written, the claim is vague and indefinite. For example, it is unclear whether the "enzymes" synthesize the neurotransmitter or the precursors. Furthermore, it is unclear if the isolated nucleic acid must encode a trophic factor as well as a neurotransmitter or precursor or enzyme.

Base claim 28 recites the phrase, "minimal CMV promoter which has been modified so as to contain from 1 to 10 sequences of site for binding a tTA factor (tetOp)". First, the claim is grammatically incorrect, because an article is missing before the term "site". In addition, the claim recites the term, "minimal CMV promoter" which is not particularly defined in the specification. (Spec. p. 12, ¶ 1; incorporating by reference a nonpatent literature document in referring to minimal promoters).

Does applicant mean a CMV promoter lacking enhancer elements or does minimal CMV promoter mean that said promoter contains the prescribed "tetOP" sequences? As written, it is unclear how the claim is to be interpreted in determining the claims' metes and bounds.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

2. Claims 20-27, 29 and 31-32 are rejected under 35 U.S.C. 102(b) as being anticipated by Bujard et al. (US 5650298; see whole document; hereinafter '298 patent).

This rejection is of record, as applied to claims 1-4 (canceled), but is repeated in salient part where applicable to the pending claims. Applicant's arguments will be addressed immediately below. (Infra, Response to Arguments).

The claims are generally drawn to a tetracycline regulated expression system. More particularly, the claims are drawn to an isolated nucleic acid occurring in any cell or mammalian cell, where a first region encodes a tetracycline operon transactivator, a second region comprises a nucleic acid of interest under control of a tetracycline sensitive promoter, where both regions are arranged in the same orientation, and said nucleic acid can be comprised in a vector. Further limitations are drawn to a third region placed in between the first and second, where the third region restricts transcriptional interference.

Additional embodiments are directed to the promoter linked to the tTA is a β actin promoter, the protein of interest can be "trophic factors" which is interpreted as broadly as reasonable to mean any protein involved in growth/nutrition.

The '298 patent teaches a tetracycline-regulated expression system to be inserted into a mammalian cell (e.g. mouse) by means of homologous recombination. (e.g. Abstract, Fig. 13A-B, col. 5, ll. 1-25). As is explicitly depicted in Figs. 13A and B, the '298 patent teaches a nucleic acid molecule comprising the tTA expression system comprises kilobase size fragments of the gene of interest, which would intrinsically contain the required promoter region. For example, a transcriptional terminator is located downstream (e.g. Figs. 13A-B), after which in the same orientation is a gene of interest under control of a minimal phosphoglycerate kinase (PGK) promoter (Id.). Further, it is explained that a DNA construct contains a fusion of sequences that normally flank the endogenous gene and contain promoter sequences are fused to the tTA system. (col. 20, ll. 16-22).

Alternatively, the tetracycline-regulated system can be under spatial and temporal control of the β-actin promoter. (e.g. col. 23, l. 2). Furthermore, the construct comprises a third region, which is arranged in between which restricts transcriptional interference, e.g. tTA transactivator. (col. 20, last ¶ bridging to col. 21). In addition, the protein of interest that can be thus regulated can be virtually any desired protein, including growth/nutrition related proteins such as erythropoietin, growth hormone, dystropin and tyrosine hydroxylase (e.g. col. 28, ll. 50-60). Therefore, the '298 patent anticipates the rejected claims.

Response to Arguments

Applicant's arguments that the claims are patentable over the '298 patent have been considered but are not deemed persuasive. The contention is that the '298 patent teaches two different embodiments that must be considered separately. (Remarks, p. 9, bottom ¶). Further, special reference is made to one embodiment of the '298 patent that indicates the construct excludes the promoter region for the target gene. (Remarks, p. 10, top, citing col. 3, ll. 34-42).

Applicant's argument is predicated on the '298 patent teaching a single embodiment. However, the '298 patent teaches several embodiments, where at least some embodiments teach every limitation that is claimed in the instant Application. For example, the '298 patent teaches in an alternative embodiment that a DNA construct (i.e. vector) can contain a fusion between the tTA system and flanking sequences commonly referred to as promoter sequences. (e.g. col. 20, ll. 14-36). Furthermore, the disclosed nucleic acid structure as depicted in Fig. 13A and B reads on the claimed invention, irrespective of what is the '298 patent's intended purpose or use the disclosed nucleic acid constructs and irrespective of how it was made. Moreover, where sequences of a flanking region are several kilobase in length, the construct would necessarily or intrinsically, at least with respect to some genes, contain the promoter region for that gene. In sum, the '298 patent anticipates the rejected claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

3. Claims 20-27, 29, 31-33 and 36 are rejected under 35 U.S.C. 102(b) as being unpatentable over Bujard et al. (US 5650298; see whole document; hereinafter '298 patent), further in view of Corti et al. (NeuroReport, 1996; 7:1655-1659).

The claims are interpreted consonant with the interpretations set forth in discussion of the rejection under the 35 U.S.C. 102. (Supra, rejection no. 2). Additional embodiments, are drawn to the transcription terminator being an upstream mouse sequence (UMS), that 1-10 sequences of the tet-responsive (tetOP) elements are present in the second promoter which is a minimal CMV promoter and that an isolated nerve cell can contain the claimed nucleic acid molecule borne in a recombinant adenovirus.

The '298 patent also teaches that the second promoter can be a CMV minimal promoter (i.e. without enhancer elements) that contain up to seven tetOP elements. (e.g. col. 5, ll. 60-66; col. 6, ll. 55-65).

The '298 patent, although indicating any human cell can be any mammalian cell, does not expressly indicate nerve cell, nor does the '298 patent indicate that the tet-expression system taught, can be incorporated in an adenoviral vector. Furthermore, the '298 patent doesn't specifically indicate that the transcription terminator can be a UMS, but does indicate that any suitable transcription terminator (affecting the tet-regulated expression) as known in the art can be used. (e.g. col. 21, ¶ 1).

However, Corti et al. generally teaches a tet-expression system (tTA system) in nerve cells. More particularly, Corti et al. teach a construct that comprises the tTA system under control of a CMV promoter as well as a reporter gene under a minimal CMV promoter with the two transcription units being separated by a UMS sequence, all oriented in the same direction. Corti et al. teach a tetracycline regulatory system for the regulation of genes introduced into the CNS. (e.g. p. 1658, col. 2, last ¶).

Therefore, it would have been obvious for one of skill to use the UMS transcription terminator in the tetracycline-expression system as taught by the '298 patent. One of skill would have been motivated to make this minor modification by virtue of the express statement in the '298 patent that other transcription terminators can be used. As Corti et al. teach, the UMS transcription terminator was well known at the time of invention. Therefore, the artisan would have been motivated to use transcription terminators, such as UMS, to expand the range of terminators to be used in the tTA-regulated system. Given the skill and knowledge at the time of invention, there would have been a reasonable expectation of success to use the UMS as one of many transcription terminators in the tTA-regulated system.

In addition, Corti et al. indicate that the vector-borne tTA system can be used in nerve cells. The '298 patent indicates that the tTA system taught can be used in any mammalian cell. Either the '298 patent or Corti et al. teach a vector-borne tTA system, with the only variation in the constructs being that Corti et al. teaches the first promoter being a viral CMV promoter. However, this variation is also explicitly taught in the '298 patent. (e.g. col. 22, last ¶ bridging to col. 23; indicating that the first promoter can be a constitutive promoter such as CMV, as is also taught by Corti et al.). Therefore, it would have been obvious to use the '298 patent's vector-borne tTA system in nerve cells. One of skill would have been motivated to do such, so as to broaden the scope of potential cells in which the tTA system can be used to regulate gene expression. Given the skill and knowledge at the time of invention, there would have been a reasonable expectation of success to utilize a tTA system as taught by the '298 patent in nerve cells.

4. **Claims 20-27, 29, 30-33 and 36-37 rejected under 35 U.S.C. 103(a) as being unpatentable over Bujard et al. (US 5650298; see whole document; hereinafter '298 patent) and Corti et al. (NeuroReport, 1996; 7:1655-1659), further in view of Hu et al. (Can. Res. 1997; 57:3339-3343).**

Additional embodiments are directed to the tTA system being on an adenoviral vector. Neither the '298 patent or Corti et al. teach that the vector comprising the tTA system can be an adenoviral vector.

However, Hu et al. teach a tTA system comprised on an andenovirus vector. Just as in the construct taught by Corti et al. and the '298 patent, the Hu et al. construct contains a pCMV

constitutive promoter driving tTA and a tTA-responsive promoter, the minimal CMV promoter driving a gene of interest. (e.g. p. 3340, Fig. 1).

Therefore all three references teach a tTA system for gene expression. It would have been obvious to incorporate the tTA system in an adenovirus as a vector to effectuate use of the tTA system in a particular cell. one of ordinary skill in the art would have been motivated to do so to obtain the benefit of expanding the range of cells that can be transfected using the tTA regulatory construct. Given the knowledge and skill at the time of invention, there would have been a reasonable expectation of success to incorporate the tTA regulatory construct of either the '298 patent or Corti et al. in an adenoviral vector as taught by Hu et al.

Conclusion

No claims are allowed. Claim 35 has not been treated on the merits as being improperly multiple dependent.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ray Akhavan whose telephone number is 571-272-0766. The examiner can normally be reached between 8:30-5:00, Monday-Friday. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, PhD, can be reached on 571-272-0781. The fax phone numbers for the organization where this application or proceeding is assigned are 571-273-8300 for regular communications and 703-872-9307 for After Final communications.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully submitted,

Ray Akhavan/AU 1636

GERRY LEFFERS
PRIMARY EXAMINER